

turn, significantly upregulated SOCS3, an inhibitor of NF- κ B signaling cascade. The upregulation of SOCS3 may be responsible for the sustained anti-inflammatory effects of DCS. This was also evident by the down-regulation of pro-inflammatory and matrix-proteinase genes by micro-array analysis of the chondrocytes subjected to 1) transient DCS over an extended time period *in vitro* and 2) exercise during the early stages of the progression of OA in rat knees.

Conclusions: The data suggest that dynamic biomechanical signals attenuate inflammation in chondrocytes not only by inhibiting the activation of NF- κ B, but also by suppressing the NF- κ B activity through the activation of SOCS3 via IL-11-mediated JAK3-STAT3 signaling. These observations further underscore the mechanisms of short and gentle DCS or exercise regimens in exerting sustained anti-inflammatory effects *in vitro* and *in vivo*.

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ASSOCIATION OF ATHEROSCLEROSIS WITH PRESENCE AND PROGRESSION OF OSTEOARTHRITIS OF THE KNEE AND HAND: THE ROTTERDAM STUDY

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Purpose: Atherosclerosis is an important feature of cardio-metabolic disorders and although some studies have indicated that atherosclerosis is associated with osteoarthritis (OA), they are few in number, often lack sufficient power and are cross-sectional only. Hence, it is unclear whether atherosclerosis and OA are associated, either as concurrent diseases due to a common aetiology or causally related. We examined whether vascular alterations are associated with the presence, incidence and progression of OA of the knee, the hip, and the different hand joints in a large prospective cohort study.

Methods: The study comprised 5,650 participants, aged 55 years and older, from the population-based Rotterdam Study. Based on previous literature, data was analyzed for men ($n=2,372$) and women ($n=3,278$) separately. We scored X-rays of the knee, hip and hand using the Kellgren & Lawrence (K&L) score for OA at baseline, after a mean follow-up of 6.6 years and 10 years. Measures of atherosclerosis (carotid intima media thickness (IMT) and presence of carotid plaque) and data on covariates (age, body mass index, diabetes, hypertension, total cholesterol/HDL and smoking) were collected at baseline. A multivariate logistic regression model with generalized estimated equations was used to analyze the association between measures of atherosclerosis and the presence and overall progression (incidence and progression combined) of OA of the hand, knee and hip joints. In the multivariate analyses on overall progression of OA, we adjusted for follow-up time and K&L score at baseline next to the other covariates. Crude and adjusted odds ratios with 95% confidence intervals were calculated.

Results: In women, significant associations between measures of atherosclerosis and prevalence of knee OA and hand OA were found; carotid intima media thickness (IMT) with knee OA (adjusted odds ratio (aOR) 1.7 (1.1 - 2.7)), carotid plaque with distal interphalangeal (DIP) OA (aOR 1.4 (1.2 - 1.7)) and with metacarpophalangeal (MCP) OA (aOR 1.5 (1.1 - 2.2)). No associations were found for hip OA. Results from prevalence of MCP OA were confirmed in overall progression of MCP OA in women; carotid intima media thickness (IMT) with overall progression of MCP OA (aOR 2.9 (1.2 - 6.9)). Results from prevalence of knee OA in women tended toward confirmation in overall progression of knee OA, but were only borderline significant. However, for overall progression of hip OA in women, odds ratios tended toward a protective effect. In men, no significant associations were found.

Conclusions: In the present study we found an association between atherosclerosis and OA of the knee, MCP and DIP joints in women. Our results indicate that in women atherosclerosis and OA of the knee and hand are at least concurrent diseases that share risk factors and there might be a role for atherosclerosis in the progression of the disease as well. Further studies are required to clarify the nature of the association found and the joint differences identified.

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IMPLICATION OF CIRCULATING NATURAL ANTIBODIES AGAINST ANGIOTENSIN-CONVERTING ENZYME IN THE PERIPHERAL BLOOD SERA OF PATIENTS WITH KNEE OSTEOARTHRITIS: A MARKER OF DISEASE ACTIVITY OR REGULATOR OF INFLAMMATION AND PAIN?

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Purpose: Knee osteoarthritis (kOA) results, at least in part, from overloading and inflammation leading to cartilage degradation. Inflammatory mediators such as bradykinin, histamine, prostaglandins, lactic acid, substance P, and calcitonin gene-related peptide are released into the joint. Innate immune system activation, best documented in responses to pathogens, likely plays a role in induction of inflammatory mediators in kOA. Angiotensin-converting enzyme (ACE) plays an important role in a number of inflammatory and immune related disorders. The aim of our work was to study the expression of natural antibodies against ACE (ACE-NA) in the peripheral blood sera of kOA patients and found a correlation between serum ACE-NA level and other markers.

Methods: Sera were obtained from 57 patients with primary kOA fulfilling the American College of Rheumatology criteria and 57 ethnically matched healthy controls. All kOA patients had involvement of the knee joint with typical radiographic changes graded Kellgren & Lawrence classification. The presence of ACE-NA was examined by a novel ELISA. Affinity chromatography yielded ACE-NA (revealed upon Ion-exchange Chromatography on QAE Sephadex) from both kOA patients and healthy individuals. Expression of cytokines was measured by Bio-Plex Human Cytokine Assay (Bio-Rad Inc, Hercules, CA, USA).

Results: ACE antibodies (IgM, IgG, IgA), reacting with ACE tested, were present in the sera of kOA patients as well as in the sera of normal individuals. Affinity chromatography yielded three (IgM, IgG, IgA) isotypes of ACE-specific NA from the both kOA patients and healthy individuals. Purified ACE-NA displayed the expected characteristics and was functionally fully active. No statistically significant differences were found between ACE-IgG and ACE-IgA for kOA patients and healthy individuals. The level of ACE-IgM in the sera from the kOA patients was significantly higher than those from the control group ($P<0.005$). ACE-IgM was expressed at higher levels in kOA than in other OA. No correlation was found between serum ACE-IgM level and patient's age and body mass index. There was a positive correlation between serum ACE-IgM level and expression of pain-associated molecules such as inducible nitric oxide synthase ($r=0.652$; $P<0.01$), IL-6 ($r=0.815$; $P<0.05$) and proinflammatory cytokine as such IL-1 ($r=0.789$; $P<0.01$).

Conclusions: We first identified ACE-NA in the sera of kOA patients. The ACE-IgM test gives significant information about kOA patients. Serum ACE-IgM is a good discriminator between kOA patients versus patients with other OA and healthy people. Serum ACE-IgM level may help to classify OA patients. We shown that their could be used a specific marker for diagnosis and prognosis of primary kOA. Renewed interest in ACE antibodies opens up a new area for kOA diagnostics and therapeutics.

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MACROPHAGES ARE MODULATED BY FACTORS SECRETED BY ADIPOCYTES

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Purpose: Obesity has been associated with development and progression of osteoarthritis. Although the biological mechanisms underlying this association are unknown, several studies have indicated that adipose tissue secretes a large variety of soluble factors that can influence whole-body metabolism. We have recently shown that the infrapatellar fat pad (IFP), an adipose tissue organ in the knee joint, is a source of inflammatory mediators that could influence joint pathology. Moreover, we identified obesity-related changes in cytokine release by IFP. Both adipocytes and immune cells present in IFP could constitute the source of these inflammatory mediators. Among IFP-infiltrating immune cells, macrophages are